DOI:
10.1002/ejp.1480

Document Version
Peer reviewed version

Change in Fatigue in Acceptance and Commitment Therapy-Based Treatment for Chronic Pain and Its Association with Enhanced Psychological Flexibility

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejp.1480

This research is independent work supported in part by the National Institute for Health Research (NIHR Postdoctoral Fellowship, Dr Whitney Scott, PDF-2015-08-059). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. The authors received no specific funding for this work.

The authors declare that there is no conflict of interest.

Significance: To our knowledge, this is the first study investigating the association between fatigue interference and psychological flexibility processes in chronic pain, and the first one investigating fatigue interference as a predictor of functioning in chronic pain following Acceptance and Commitment Therapy (ACT)-based treatment. Findings of the study provide preliminary evidence for the association between ACT and fatigue in people with chronic pain and support the potential benefit of ACT for people with comorbid chronic pain and fatigue.

Abstract:

Fatigue is commonly reported by people with chronic pain. The purpose of the current study was to examine Acceptance and Commitment Therapy (ACT), based on the Psychological Flexibility (PF) model, for fatigue in chronic pain. This study included 354 adults attending an interdisciplinary ACT-oriented treatment for chronic pain. T-tests and analyses of clinically meaningful change were used to investigate participant improvements in fatigue interference after the treatment. Pearson's correlations and hierarchical regressions were conducted to investigate associations between improvement in fatigue interference and improvements in PF processes. Finally, mixed effects models were used to explore associations between baseline fatigue interference and changes in treatment outcome measures. Participants improved in fatigue interference (*d*=.37), pain, some PF

processes, and daily functioning (*d*=.18-1.08). 39.7% of participants demonstrated clinically meaningfully improvements in fatigue interference. Changes in fatigue interference was associated with changes in pain, PF processes and daily functioning, |*r*|= .20-.46. Change in fatigue interference was associated with change in pain acceptance independent of change in pain, *β*=-.36, *p*<.001. However, baseline fatigue interference did not predict any treatment outcome. Overall, people with fatigue appeared to benefit from the ACT-oriented interdisciplinary treatment for chronic pain, and relatively higher levels of fatigue did not appear to impede this benefit. ACT-based treatments may benefit people with chronic pain and fatigue. Future studies including experimental designs, and studies investigating other PF processes, are needed to better understand the utility of ACT for co-morbid fatigue and pain.

Key words: chronic pain; fatigue; co-morbidity; Acceptance and Commitment Therapy; Psychological Flexibility

1. Introduction

Fatigue is a subjective symptom, described as a sensation of weakness, lack of energy or tiredness, and in some cases a sustained exhaustion associated with a decreased capacity for physical and mental work (Hewlett et al., 2005; Berrios, 1990). Significant fatigue is commonly reported by people with chronic pain (Covington, 1991; Wolfe et al., 1995; Creavin et al., 2010; Craig et al., 2013). People with more severe chronic pain have nine times the odds of having chronic fatigue (Craig et al., 2013). Fatigue is more prevalent in participants with chronic widespread pain, compared to those without pain (Creavin et al., 2010). In some conditions where chronic pain is a primary symptom such as fibromyalgia, fatigue is a defining feature (Mengshoel et al., 1995; Wolfe et al., 1996; Wolfe et al., 2016; Dorado et al., 2017). Fatigue is perceived as among the "most bothersome" symptoms by people with fibromyalgia (Arnold et al., 2008). Fatigue and chronic pain

are both associated with significant suffering (Breivik et al., 2006; Opheim et al., 2018), and socioeconomic costs (Reynolds et al., 2004; Breivik et al., 2013). The co-occurrence of these conditions can potentially lead to additional detrimental personal and social impacts (Van Damme et al., 2018).

Cognitive Behavioural Therapy (CBT) is an evidence-based treatment for chronic pain (Bernardy et al., 2010; Williams et al., 2012). However, evidence regarding the utility of CBT in comorbid chronic pain and fatigue remains limited. In a systematic review of CBT for fibromyalgia syndrome (Bernardy et al., 2010), fourteen randomized-controlled trials (RCTs) were identified, among which only four investigated fatigue, using solely a visual analogue scale to assess fatigue. No significant reduction in fatigue was observed at post-treatment or follow-up in these studies. There is limited evidence upon which to judge the potential efficacy of CBT for comorbid pain and fatigue.

A specific form of CBT, Acceptance and Commitment Therapy (ACT; Hayes, Strosahl, & Wilson, 2011), may be useful to manage co-morbid chronic pain and fatigue. ACT is essentially widely applicable and not designed around specific diagnoses, and sometimes called “transdiagnostic.” It has achieved promising results for improving quality of life and functioning in people with a wide range of conditions, including anxiety, depression, and other physical and mental health problems (A-Tjak et al., 2015). ACT does not focus on particular symptoms but on common processes underlying the ways that different symptoms exert their distressing and disabling impacts. ACT may be well suited to meet the treatment needs of people with co-occurring pain and fatigue.

ACT is based on a unified model of psychological health and psychotherapy, called the Psychological Flexibility model (PF; Hayes, Strosahl, & Wilson, 2011). Psychological flexibility is the ability to be consciously in contact the present moment, to be open to challenging experiences without unhelpful

defence, and to persist or change one's behaviours, in the service of one's goals and values (Yu & McCracken, 2016). The PF model includes a set of practical organizing terms reflecting key therapeutic processes: acceptance, present moment awareness, cognitive defusion, self-as-context, committed action, and values-based action, which are also summarised as "open, aware, active" (Hayes, Villatte, Levin, & Hildebrandt, 2011).

ACT and related approaches have been widely used in the treatment for chronic pain, (Hann & McCracken, 2014; Veehof et al., 2016; Simpson et al., 2017), including in people experiencing chronic pain and fatigue in the context of fibromyalgia (Wicksell et al., 2013; Steiner et al., 2013; Luciano et al., 2014; Ljótsson et al., 2014; Simister et al., 2018), and for people whose primary complaint is fatigue (Jacobsen et al., 2017). In these studies, ACT appears beneficial for a range of outcomes, such as pain, fatigue severity, the functional impact of fatigue, mood, fibromyalgia symptoms and impact, disability, and quality of life. In one pilot study of ACT-consistent treatment for fibromyalgia a reduction in fatigue was observed immediately after the treatment (*d*=.75), and at the 6-month follow-up (*d*= .62) (Ljótsson et al., 2014). However, the benefits for fatigue in the context of chronic pain more generally (i.e., not specific to fibromyalgia) remain unknown as do relations between changes in PF in relation to change in fatigue.

Although people with chronic pain benefit from ACT-based treatments on average, no moderator variables have been identified that consistently predict responsiveness to ACT for chronic pain (Gilpin et al., 2017). To further understand the impact of ACT for people with complex, multi-comorbid conditions, further analyses to understand different individual outcomes from ACT are needed. Here fatigue has not been studied as a baseline characteristic that could influence outcomes associated with ACT. It is plausible that chronic pain suffers with high fatigue might benefit more from ACT-based treatment compared to those without high fatigue. This is based on a

previous study which found a reduction in fatigue interference (d=.75) after ACT-based treatment for conditions where chronic pain is a primary symptom (Ljótsson et al., 2014). Additionally, ACT is theoretically well-suited to highly complex and transdiagnostic problems as it assumes that the same behavioural responses underlie the impact of a range of symptoms (Hayes, Strosahl, & Wilson, 2011). However, it is also plausible that high fatigue may present an additional barrier, impeding engagement, in an ACT-based treatment that encourages increased activity levels. This could reduce effects of treatment.

As ACT-oriented treatment does not directly target symptoms but their function, the functional impact rather than the intensity of fatigue, is important to investigate. The Fatigue Severity Scale (FSS) assesses the functional impact of fatigue and, usefully has a cut-off score to identify participants who have clinically significantly fatigue. (Friedman et al., 2010). This represents a potentially useful tool in the context of ACT.

The purpose of the current study is to examine potential benefits of an ACT-based interdisciplinary treatment for chronic pain for people with comorbid pain and fatigue. Three specific objectives were (1) to investigate if fatigue interference improves, alongside PF processes and daily functioning after the treatment, (2) to investigate if the improvement in fatigue interference is correlated with improvements in theorized therapeutic processes of ACT and, (3) to explore if baseline fatigue interference predicts improvements in daily functioning, to essentially see whether people with fatigue seem to benefit more or less than others in treatment. We predicted that fatigue interference would improve following the treatment, alongside pain, PF processes, and daily functioning; and that improvements in fatigue interference would be correlated with improvements in PF processes. The association between baseline fatigue interference and changes in daily functioning was exploratory and thus a specific prediction was not made.

2. Methods

2.1 Participants

Participants were consecutive referrals attending an interdisciplinary pain management programme at the INPUT Pain Clinic at St Thomas' Hospital in London, UK between June 2016 and September 2017. Figure 1 shows the data collection process. Table 1 shows the demographic characteristics of the participants included in the analyses.

2.2 Study Design

This was a prospective observational cohort study. All participants were assessed by a psychologist and physiotherapist to determine their suitability for an intensive, group-based, rehabilitation programme based on principles of ACT for chronic pain management. Specific eligibility criteria assessed by the multidisciplinary team included the presence of pain of at least three months duration which significantly impacted on participants' daily functioning, mood, and/or overall quality of life. The team also assessed participants' willingness to engage in a treatment approach that focuses on improving quality of life and functioning with pain rather than on reducing or controlling pain. Participants were excluded if they were seeking or waiting for further medical evaluation or treatment procedures. Participants were also excluded if they had serious and poorly controlled psychiatric problems (e.g., addiction, psychosis, PTSD), were actively suicidal, or had other problems that would make it difficult to engage safely and effectively in the group-based treatment (e.g., interpersonal difficulties, cognitive impairment). Decisions to include or exclude participants were made based on the judgements of the assessing clinicians rather than on cut-off scores on self-report questionnaires of pain, mood, and functioning.

Data for this study were collected during a period in which the service changed from a four-week programme consisting of four days per week (16 days total) to a three-week programme with five days per week (15 days total). This change was based on pragmatic needs of the service's delivery capacity, rather than on patients' performance during treatment. Participants were informed of their exact treatment duration prior to attending. Given the comparable number of days and structure of the three- and four-week programmes, we combined the data for analysis. One hundred and forty-nine participants (42.1%) completed the four-week and 205 (57.9%) completed the three-week residential treatment.

The treatment was delivered by an interdisciplinary team of psychologists, physiotherapists, occupational therapist, and nurses. Treatment was informed by ACT for chronic pain management, which aims to enhance functioning and quality of life with pain through fostering greater psychological flexibility (McCracken & Morley 2014; McCracken & Vowles 2014). Principles of ACT are applied by the different clinicians in the interdisciplinary team. Metaphors, experiential exercises, mindfulness practice, values clarification, goal-setting, and direct rehearsal are used across the disciplines to foster and shape behaviour that is "open, aware, and engaged" (Hayes, Villatte, Levin, & Hildebrandt 2011). The treatment also includes physical exercise and practical skills training. Although the treatment is generally focused on pain management, there is longstanding recognition that fatigue is a significant problem for many participants receiving treatment in this service. Throughout the programme clinicians apply ACT-based principles and strategies to reduce the impact of symptoms and other experiences that interfere with daily functioning, including pain and fatigue. Clinicians in the service attend weekly clinical development meetings to maintain and enhance the team's skills in applying ACT across the disciplines. This study was approved by the National Research Ethics Service Committee South Central – Oxford C (12/SC/0451). The study was conducted in accordance with the 1964 Declaration of Helsinki and its amendments.

2.2 Measures

Participants completed standardized measures at the beginning and end of treatment. At baseline, participants reported demographic information, including age, gender, ethnicity, education, pain duration and location, and employment status. Pre- and post-treatment questionnaires assessed fatigue interference, and standard outcomes in treatments for chronic pain, including pain intensity, pain-related interference, social and occupational functioning, and mood. As the ACT-oriented interdisciplinary does not aim to reduce pain severity, but to improve daily functioning, pain severity is investigated as a control variable/predictor in the current study. The questionnaires also assessed facets of psychological flexibility which are theoretically-relevant processes of ACT for chronic pain. These process variables were chronic pain acceptance, committed action, and cognitive fusion. There is currently no efficient and well-validated way to examine all PF processes without a considerable burden on respondents or significant concern about statistical power due to sample size. Therefore, three psychological processes (pain acceptance, cognitive defusion, and committed action) were selected to assess PF in this study, as they clearly reflect core processes and derive from well-validated and brief measures.

Fatigue Severity Scale (FSS): Participants completed the 9-item Fatigue Severity Scale (FSS) as a measure of fatigue severity (Krupp et al., 1989). Items include the impact of fatigue on specific domains of functioning, including physical activities and relationships (e.g., “Fatigue interferes with my work, family or social life), and the more general impact of fatigue (e.g., “Fatigue causes frequent problems for me”). Participants rated items on a 7-point scale from 1 (strongly disagree) to 7 (strongly agree). Higher scores indicate greater fatigue impact. The FSS has high internal consistency and has been associated with measures of sleep quality and depression in samples with a range of chronic illnesses (Friedman et al., 2010). The recommended cut-off of a total score of 36 from the

FSS was applied to identify participants with clinically significantly fatigue (Friedman et al., 2010). The reliability

of the scale in the current study was, α=.96.

Pain Intensity: Participants rated the average intensity of their pain over the past week using an 11-point numerical rating scale with the endpoints 0 (no pain) and 10 (extremely intense pain).

Brief Pain Inventory—Pain Interference Subscale (BPI): The BPI pain interference assesses the impact of pain on participants' functioning in the domains of general activity, mood, walking, work, relationships, sleep, and enjoyment of life. Participants rate seven items on an 11-point scale from 0 (does not interfere) to 10 (completely interferes) (Cleeland & Ryan 1994). Scores are produced by taking the average of the seven items, with higher average scores reflecting greater pain-related interference. The BPI interference subscale is widely used as an outcome measure in studies of chronic pain (Dworkin et al. 2005). The reliability

of the scale in the current study was, α=.86

Work and Social Adjustment Scale (WSAS): The WSAS is a measure of social and occupational functioning, which includes functioning in work, home management, private and social leisure activities, and close relationships (Mundt, Marks, Shear, & Greist 2002). An example item is "Because of my condition, my ability to form and maintain close relationships with others, including those I live with, is impaired." (Mundt et al., 2002). Participants rated five items using a nine-point scale with the endpoints 0 (no impairment) to 8 (very severe impairment). The WSAS has been

shown to be reliable and valid for use in participants with persistent physical symptoms, such as fatigue (Cella, Sharpe, & Chalder 2011). The reliability

of the scale in the current study was, α=.77

Patient Health Questionnaire Depression Module (PHQ-9): The PHQ-9 is a nine-item screening measure for symptoms of depression (Kroenke, Spitzer, & Williams 2001). The first two PHQ-9 items assessing low mood and anhedonia are considered the hallmark symptoms of depression (Schmidt & Tolentino, 2018). The PHQ-9 also measures "somatic" features of depression, including fatigue, sleep problems, and weight changes (one item each). Participants rate the items to reflect the frequency with which they have experienced each symptom over the past two weeks, with endpoints from 0 (not at all) to 3 (nearly every day). The PHQ-9 is a well-validated and widely used measure of depression symptoms, including in samples with chronic pain (Kroenke et al. 2001). The reliability of the scale in the current study was, α=.82

Chronic Pain Acceptance Questionnaire-8 item version (CPAQ-8): Chronic pain acceptance describes engaging in desired activities with pain present and refraining from efforts to control or avoid pain when such efforts have not been helpful (McCracken, Vowles, & Eccleston 2004). The CPAQ-8 is a validated brief version of the original CPAQ measure of pain acceptance (Fish, McGuire, Hogan, Morrison, & Stewart 2010). The CPAQ-8 retains the original CPAQ structure and measures pain willingness (e.g., "Keeping my pain level under control takes first priority whenever I am doing something) and activity engagement (e.g., "I am getting on with the business of living no matter what my level of pain is"). Participants rated items on a seven-point scale from 0 (never true) to 6 (always true). CPAQ-8 total scores were used, with higher scores reflecting greater pain acceptance. The CPAQ-8 has good internal consistency and has been associated with improved mood and

functioning in people with chronic pain (Baranoff, Hanrahan, Kapur, & Connor 2014; Fish et al. 2010). The reliability of the scale in the current study was, α=.69.

Committed Action Questionnaire-8 item version (CAQ-8): Committed action reflects persistent and flexible pursuit of goals that are guided by one's values (Hayes, Levin, Plumb-Vilardaga, Villatte, & Pistorello 2013). This includes continuing in goal-directed activities in the presence of pain and other challenges, as well as a willingness to changes one's goals when they are no longer helpful (Hayes et al. 2013). An example item includes "I can remain committed to my goals even when there are times that I fail to reach them" (McCracken 2013). The CAQ-8 is a reliable and valid shortened version of the original CAQ (McCracken 2013), both of which have been validated in participants with chronic pain (McCracken, Chilcot, & Norton 2014). Participants rated the eight items using a seven-point scale 0 (never true) to 6 (always true). When summed, higher total scores indicate higher levels of committed action. The reliability of the scale in the current study was, α=.80.

Cognitive Fusion Questionnaire (CFQ): Cognitive fusion describes challenges in separating one's thoughts from the events or person to which they refer (Hayes et al. 2013). Cognitive defusion strategies within ACT aim to alter the function of thoughts to reduce their excessive influence on behaviour, particularly when such influence contributes to behaviour patterns that are unhelpful or inconsistent with one's values (Hayes et al. 2013). On the CFQ, participants rated seven items from 1 (never true) to 7 (always true). Consistent with the initial validation studies, the CFQ was scored such that higher scores reflect greater *fusion* (e.g., "I get upset with myself for having certain thoughts"; Gillanders et al. 2014; McCracken, DaSilva, Skillicorn, & Doherty 2013). Therefore, we expected the CFQ and measures of interference and distress to be positively associated, while we expected negative correlations with the other process measures of psychological flexibility. Previous studies

indicate that the CFQ has good internal consistency and is associated with chronic pain outcomes. The reliability of the scale in the current study was, α=.95

2.4 Statistical analysis

Skewness, kurtosis, histograms, and Q-Q plots for each variable were examined for normality. Scatter plots for all variables involved in correlation analyses were examined for linearity. The total scores of all measures were considered normally distributed. No significant nonlinear relation was found. Additionally, participants who did and did not provide post-treatment data were compared on all demographic, pain, PF process variables (CPAQ-8, CFQ, CAQ-8), and outcome variables (FSS, BPI, WSAS, PHQ) at baseline, using Chi-square tests for categorical variables and independent samples t-tests for continuous variables.

2.4.1 Changes in fatigue, pain, PF processes, and daily functioning after the ACT-oriented interdisciplinary treatment

Changes in study variables from baseline to post-treatment were examined by paired-samples t-tests. Cases with missing data were deleted analysis by analysis. Within-subject effect sizes were calculated using the equation recommended for repeated measures to avoid inflation of effect sizes associated with non-independent design (Nakagawa & Cuthill, 2007): $d=t_{\text{paired}}\sqrt{2(1-r_{12})/n}$ (Dunlap et al. 1996). Cohen's (1988) thresholds for interpreting effect sizes were adopted: *d*=.20 is considered as small effect size, *d*=.50 medium, *d*=.80 large. Clinically meaningful change was also examined for fatigue interference scores at post-treatment. Participants whose raw change scores were greater than one half of a standard deviation from their baseline score for each outcome variable were coded as 'meaningfully improved'. Those whose scores did not improve by half a standard deviation were coded as 'not meaningfully improved', while those who worsened by

greater than half of a standard deviation were coded as 'meaningfully worsened'. In a systematic review of interpretation of minimal important difference in health-related quality of life (Norman, Sloan, & Wyrwich, 2003), half a standard deviation was suggested as the threshold of meaningful change for health-related self-report measures for chronic diseases.

2.4.2 Correlations between changes in fatigue interference, pain, PF processes and daily functioning.

Pearson correlations were conducted with residualized change scores for all variables to examine the associations between changes in study variables. Missing data were deleted pairwise. Standardized residualized change scores were calculated for the changes from baseline to post-treatment for fatigue, pain, PF process variables and other outcome variables. For each variable, baseline scores were used to predict post-treatment scores, and residualized change scores were calculated as the differences between predicted and observed scores. Cohen's (1988) thresholds for interpreting effect sizes were adopted: *r*=.10 is considered as small effect size, *r*=.30 medium, *r*=.50 large.

Following the correlation analyses, hierarchical multiple regressions were conducted to examine the independent role of each process variable in relation to change in fatigue interference. Missing data were deleted pairwise. In these analyses change scores on process variables were independent variables and change scores for fatigue was the dependent variable. For the hierarchical regression model, demographic variables were simultaneously entered step-wise into the first block, and pain intensity was force entered into the second block. A recent comprehensive examination of the structure of the PF model using confirmatory factor analyses in a large chronic pain sample suggested that a general factor reflecting openness explained variance across all measures of PF (Scott et al., 2015). Therefore, pain acceptance was forced entered into the third block, and

cognitive fusion and committed action were forced entered simultaneously in the last block.

2.4.3 The association between baseline fatigue interference and changes in daily functioning after the treatment

Linear mixed effects modeling with maximum likelihood estimates, was used to examine the association between baseline fatigue interference and changes in other outcome variables after the treatment. Mixed effects models include fixed as well as random effects to analyze variable changes between and within individuals over time. Mixed effects models allow for flexibility in specifying variance-covariance structures and modeling trends in missing data important for conducting intention to treat analyses. In the current study, an effect of time (baseline/post-treatment) and baseline fatigue scores, as well as the interaction between time and baseline fatigue scores (fatigue*time) were included as fixed effects in the mixed models, with random intercepts and fixed slopes. For the time variable, baseline scores were coded as “0”, and post-treatment scores were coded as “1”. Baseline fatigue scores were standardized. For further analyses, baseline fatigue scores were recoded as clinically significant fatigue or not, according to the recommended cut-off of a total score of 36 from Fatigue Severity Scale (Friedman et al., 2010). Additionally, the interactions identified in mixed effects models were plotted, and people who did and did not show clinically significant fatigue were compared at baseline and post-treatment on each relevant outcome variable, using independent sample t-tests.

3. Results

3.1 Preliminary analysis

Two participants scored out range at baseline on FSS, one on the WSAS, two on the CFQ, and at post-treatment one on the BPI, one on the CPAQ, one on the CFQ, and the items of these scales that were scored out of the scoring range were treated as missing data. One participant (0.3%) did not provide data on pain intensity, while participants missing data on other variables were nine FSS (2.5%), one BPI (0.3%), one WSAS (0.3%), seven CPAQ (2%), nine CFQ (2.5%), and eight CAQ (2.3%). At post-treatment, 53 (15%) participants did not provide data on pain intensity. Missing data on other variables were 58 FSS (16.4%), 52 BPI (14.7%), 52 WSAS (14.7%), 54 PHQ (15.3%), 57 CPAQ (16.1%), 58 CFQ (16.4%), 57 CAQ (16.1%). Overall, the low level of missing data is not considered to result in bias.

Participants who did and did not provide post-treatment data did not show any difference in any demographic variable, except for working status (working/not working), χ^2 =4.42, *p*=.035, and primary pain site (generalized pain or not), χ^2 =6.17, p=.013. 88.8% (n=103) of participants who were working (n=116) provided data at post-treatment, while 79.7% (n=181) of participants who were not working (n=227) did. 86.4% (n=197) of participants without generalised pain (n=228) provided data at post-treatment, while 75.2% (n=76) participants with generalized pain (n=101) did. The two groups of participants did not differ on any process or outcome variables at baseline, except for pain acceptance. Participants who provided data at post-treatment (M=17.02, SD=7.49) showed significantly greater pain acceptance at baseline, compared to those who did not (M=14.23, SD=7.20), *t* (345) =-2.59, *p*=.01.

3.2 Change in fatigue interference, pain, PF processes, and daily functioning

After treatment, scores on fatigue interference significantly decreased with a small effect size (*d*=.37). Pain intensity significantly decreased, with a medium effect size (*d*=.50). Scores on outcome variables including pain-related interference, work and social adjustment, and depression, all significantly decreased, with medium to large effect sizes (*d*=.65-1.08). Scores on pain acceptance (*d*=.74) and committed action (*d*=.18) significantly improved. The change in pain acceptance was a medium effect size. While significant, the change in committed action was less than a small effect. However, cognitive fusion did not change significantly. Table 2 shows the results from the T-tests comparing baseline scores and post-treatment scores for each variable.

After treatment 39.7% (N=116) of the participants clinically meaningfully improved in fatigue interference, while 13.4% (N=39) clinically meaningfully worsened. 46.9% (N=137) of participants did not change in fatigue interference to a clinically significant extent.

3.3 Associations between changes in fatigue interference, and pain, PF processes and daily functioning

Changes in fatigue interference significantly correlated with changes in pain severity, pain acceptance, cognitive fusion, and committed action, in the expected direction, with small to medium effect sizes, as well as with changes in daily functioning with medium effect sizes. Changes in pain and all PF process variables from baseline to post-treatment were significantly correlated with changes in all outcome variables, in the expected directions, with small to medium effect sizes. Table 3 shows the correlations between the changes in fatigue interference, pain, PF processes, and daily functioning.

Collinearity diagnostics including VIF values and condition indices were examined for possible collinearity between the independent variables of the regression models, and no considerable collinearity was identified. Changes in pain severity and pain acceptance significantly correlated with change in fatigue interference. After changes in pain and pain acceptance were controlled for, change in cognitive fusion was not significantly correlated with change in fatigue interference, while the change in committed action remained significantly correlated with change in fatigue interference. However, when Bonferroni correction was applied (critical a = .0125), change in committed action no longer correlated with change in fatigue interference to a statistically significant level. Table 4 shows the results from the regression analyses.

3.6 Mixed Linear Modelling and Analysis of Interactions

In linear mixed effects analyses time significantly predicted pain-related interference, suggesting that pain-related interference significantly decreased during the treatment, $F(1, 303.95) = 311.59$, $p<.001$. Baseline fatigue interference significantly predicted pain-related interference regardless of time, $F (1, 347.85) =9.77$, $p<.001$. The interaction of time and baseline fatigue interference also significantly predicted pain-related interference, suggesting that baseline fatigue potentially predicted the change in pain-related interference over time, $F (1, 306.77)=5.95$, $p=.015$. However, when Bonferroni correction was applied (critical a = .0125), the interaction was no longer statistically significantly associated with pain-related interference.

Time significantly predicted work and social adjustment, suggesting that work and social adjustment significantly improved after the treatment, $F (1, 301) =127.80$, $p<.001$. Baseline fatigue interference also significantly predicted work and social adjustment regardless of time, $F (1, 339.65)$ 33.59,

p<.001, but the interaction of time and baseline fatigue interference did not significantly predicted work and social adjustment, *F* (1, 303.21)=.27, *ns*.

Time significantly predicted depression, suggesting that depression significantly decreased after the treatment, *F*(1, 305.61)=262.55, *p*<.001. Baseline fatigue interference significantly predicted depression regardless of time, *F*(1, 349.32)=8.47, *p*<.01. The interaction of time and baseline fatigue interference marginally significantly predicted depression, suggesting that baseline fatigue potentially predicted the change in depression over time, *F*(1, 308.94)=4.02, *p*=.046. However, when Bonferroni correction was applied (critical a = .0125), the interaction was no longer significantly associated with depression.

Among participants who provided data at baseline, 79.7% reported clinically significant fatigue. The plots of the interactions showed generally a higher level of pain-related interference and depression in people with clinically significant fatigue at baseline, compared to those without. In addition, the plots showed a trend towards slightly greater reduction in pain-related interference and depression in people with clinically significant fatigue, compared to those without. Figure 2 and figure 3 show the plotting of the interactions.

When compared on pain-related interference, participants with clinically significant fatigue at baseline (M=7.93, SD=1.47) showed a significantly higher level of pain-related interference than those without (M=7.18, SD=1.94), *t* (78.75)= -2.89, *p*= .005. However, the difference was not significant after the treatment (M=5.76, SD=2.06, and M=5.57, SD= 2.16 respectively), *t*(294)= -.60 *p*=.551. When compared on depression, participants with clinically significant fatigue at baseline showed a significantly higher level of depression (M=18.47, SD=5.16), than those without (M=15.98,

SD=6.90), *t*(78.16)= 2.70, *p*=.008. However, the difference was not significant after the treatment (M=12.87, SD=6.05, and M=11.42, SD=6.43, respectively), *t*(292)=- 1.54, *p*=. 124.

4. Discussion

In the current study, about 80% of the participants reported clinically significant fatigue before treatment. This finding further underscores the importance of this particular line of research. About 40% of participants showed clinically meaningful improvement in fatigue interference after the ACT-oriented interdisciplinary treatment for chronic pain. Furthermore, change in fatigue interference appeared to be associated with changes in the study PF processes. Furthermore, people with elevated level of fatigue did not appear to benefit differently from the treatment compared to those without. Overall these data suggest that the PF model appears relevant for fatigue comorbid with chronic pain, and that the ACT-oriented interdisciplinary treatment is associated with improvements in fatigue interference for people receiving treatment primarily for chronic pain. It appears that fatigue is not an isolated issue among the problems encountered by those with chronic pain and may interact with other outcomes.

To our knowledge, this is the first study investigating the association between fatigue-related outcome and any PF processes in chronic pain, and the first one investigating fatigue-related outcome as a potential predictor of daily functioning in chronic pain following ACT-based treatment. This is the second study investigating improvements in fatigue-related outcome associated with ACT-oriented treatment in people with chronic pain. The results from the current study are consistent with evidence from previous treatment outcome studies suggesting that ACT-oriented treatment for chronic pain improves functioning through its theorized mechanisms, including pain acceptance and

committed action (Wicksell et al., 2010; McCracken et al., 2011; Trompetter et al., 2015; Scott et al., 2016). These results also resonate with a cross-sectional study in people with fibromyalgia, where the association between pain acceptance and functioning were observed (Yu et al., 2017), suggesting the relevance of pain acceptance to functioning in people with comorbid pain and fatigue. The results from the current study echo the results from a previous study investigating an ACT-consistent approach to fibromyalgia, where a significant reduction in fatigue interference was observed after the treatment (Ljótsson et al., 2014). Relatedly, evidence from several studies examining ACT in chronic fatigue syndrome have also showed significant reduction in fatigue after the treatment (Jacobsen et al., 2017; Brooks et al., 2011), and/or at follow-up (Densham et al., 2016; Brooks et al., 2011). In particular, an association between acceptance and fatigue was observed in one of these studies (Brooks et al., 2011).

Notably, in the currently study, cognitive fusion did not improve after the treatment, and was not associated with the improvements in daily functioning, when controlling for pain and pain acceptance. Similar results have also been observed in a previous study (Scott et al., 2017). This could reflect a limit in group-based treatment. Indeed, possibly different from some other PF processes such as acceptance and committed action, cognitive defusion may be especially difficult to achieve if not done individually. Perhaps more individualised training of higher intensity is required to shape this particular skill. We did not assess clinicians' fidelity in delivering ACT. Therefore, it is plausible that clinicians focused more on targeting pain acceptance than cognitive defusion in delivering the treatment. In an unplanned analysis, we compared participants who clinically meaningfully improved in cognitive fusion, those who clinically meaningfully worsened, and those who did not change to a clinically meaningful extent, on their baseline FSS scores; we did not observe an association between changes in cognitive fusion and baseline level of fatigue interference. It appeared that the functional impact of fatigue did not impede the improvement in

cognitive fusion. Further experimental and qualitative studies are needed to better understand the association between fatigue and its impact in relation to PF processes such as cognitive defusion and its implication for the delivery of ACT-oriented treatment in people with chronic pain and fatigue.

Our analyses of the association between baseline fatigue interference and treatment outcomes were exploratory. We initially found that baseline fatigue interference was associated with changes in pain-related interference and depression from pre- to post-treatment. However, when a more stringent statistical significance level was applied, baseline fatigue interference was no longer significantly associated with these outcomes. Participants with clinically significant fatigue interference showed higher levels of pain interference and depression at baseline, compared to those without, and this difference disappeared after the treatment. It is possible that the slightly larger reduction in pain-related interference and depression in participants who were clinically significant fatigue may have resulted from their larger opportunity for improvement. It is also possible that fatigue interference does not interact with these treatment outcomes, or that it is a highly individual matter, one not easily found in group data. Future studies investigating the associations between fatigue interference and other outcome domains, such as sleep disturbance, are needed to understand the potential benefit of ACT-oriented treatments for people with fatigue. In the meantime, these preliminary results should be interpreted with caution, particularly as there were considerably more participants with clinically significant fatigue compared to those without, which may limit the power of the comparison. Certainly, these results suggest that fatigue interference does not represent an impediment to treatment response for people with chronic pain.

It is worth noting that the measure of fatigue we used here, the FSS, is a brief, unidimensional measure of the functional impact of fatigue, which limited our ability to decipher the association between different dimensions of fatigue and daily functioning. Perhaps certain dimensions of

fatigue, such as the cognitive and physical aspects of fatigue play different roles in relation to treatment outcomes. Future studies using other assessments of fatigue, such as the Multidimensional Fatigue Inventory (Smets, Garssen, Bonke, & De Haes, 1995) are needed to further understand fatigue as a potential predictor of treatment outcomes.

Although a range of variables has been investigated as predictors or moderators of treatment effects in treatments like ACT for chronic pain, findings remain unclear (Gilpin et al., 2017). The current study is a preliminary attempt to build on this investigation. Future studies examining fatigue alongside other potential predictors of treatment outcomes, such as baseline levels of components of psychological flexibility (Gilpin et al., 2017) are needed to understand what treatment works for whom, and to develop better targeted and more effective treatments.

The effect size of fatigue interference was relatively small compared to the improvements in other treatment outcomes. This could reflect a weakness in the design or delivery of the treatment. The ACT-oriented multidisciplinary treatment was designed for chronic pain, and naturally focused less on fatigue, although fatigue is addressed to an extent. In a study of an ACT-consistent treatment for fibromyalgia, where fibromyalgia symptoms were particularly targeted (Ljótsson et al., 2014), a moderate reduction in fatigue interference measured by the FSS (d=.75) was observed after the treatment. Perhaps certain treatment components need to be enhanced, or extra treatment components targeting fatigue symptoms added, to improve the efficacy of chronic pain management treatment specifically for fatigue comorbid with pain. Again, this could also be a limitation of group-based treatment, with an essentially limited capacity to fully individualise treatment content.

Naturally, the current study has its limitations. First and foremost, the current study did not have an experimental design. Therefore, causal relations between fatigue interference, pain, PF and functioning cannot be drawn. That is, we cannot conclude that the ACT-oriented treatment studied here has led to the beneficial effect on fatigue interference and other aspects of functioning, nor that it has operated through the improvement of PF. Further studies using experimental designs and formal mediation analysis are needed to make firm conclusions on the underlying mechanism of ACT, and its association with fatigue. Secondly, the current study only included analysis of data at baseline and immediately after the treatment. The potential long-term associations between ACT and chronic pain and fatigue outcomes remain unknown, so does the course of change in fatigue interference. Studies with more frequent assessments and longer-term follow-up are needed.

All participants were referrals to an interdisciplinary pain management centre in London. The results may not apply to other treatment settings, or chronic pain populations in other geographical locations or other cultures. We did not collect data on the number of patients excluded from the programme following assessment to determine their suitability. However, audit data from the service suggest that approximately 45% of patients assessed for the programme are not eligible due to lack of readiness for the approach often due to complex psychosocial needs being prioritised (Knight, Guildford, Daly-Eichenhardt, & McCracken, 2019). Additionally, about 18% of the participants did not provide post-treatment data. As attrition did not appear to relate to our variables of interests, the potential bias in data may have been minimal. Further studies in other contexts with other patient populations are needed to investigate the generalisability of results reported here.

Only a subset of PF processes was investigated in relation to fatigue in the current study. Further studies are needed to examine the role of other PF processes, such as present moment awareness, self-as-context, and valued-based action, in relation to fatigue. Last, the ACT-informed treatment is an interdisciplinary programme guided by the principles of psychological flexibility. Therefore, it is difficult to delineate the effect of each discipline on the outcomes. Future studies with more comprehensive assessments on different aspects of treatment processes and functioning may help decipher the separate effect of each component of the treatment.

Conclusions

Fatigue comorbid with chronic pain is commonly observed and can be associated with significant personal suffering and socioeconomic cost. In the present study, an ACT-oriented interdisciplinary treatment for chronic pain was associated with improvements in fatigue interference and daily functioning, and the reduction in fatigue interference was associated with the enhanced PF processes and daily functioning. In addition, people with clinically significant fatigue interference at baseline appeared to benefit equally from the treatment, compared to those without this level of fatigue interference. These findings suggest some potential for ACT-oriented treatment to address fatigue comorbid chronic pain. Further randomised controlled trials with mediation analysis, or intensive single-case analyses, are needed to more definitely examine the utility of ACT for the fatigue comorbid chronic pain and the underlying mechanism of such treatment.

Author Contributions

All authors contributed study conception, study design, and manuscript write-up. In addition, Dr Lin Yu contributed significantly to literature search and data analyses. Professor Lance McCracken contributed significantly to data collection. All authors discussed the results and commented on the manuscript.

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Table 1 The Demographics of the Participants.

Table 2 Mean (M) and standard deviations (SD) at baseline and post-treatment, t values, degrees of freedom, effect sizes (*d*), and p values for baseline to post-treatment changes on study variables.

Table 3 Pearson's r and number of participants included in each analysis (N) for the correlations between residualized change scores for fatigue, pain and psychological flexibility processes (pain acceptance, defusion, and committed action), and daily functioning (pain interference, work and social adjustment, and depression).

Table 4 Hierarchical regressions with change in pain severity, pain acceptance, cognitive fusion, and committed action as independent variables, and change in fatigue as dependent variable.

Figure 1 Flowchart of data collection process

Figure 2 Plot of the Time*Baseline Fatigue Interference Interaction in Relation to Pain Interference

Figure 3 Plot of the Time*Baseline Fatigue Interference Interaction in Relation to Depression

Table 1 The Demographics of the Participants.

		Mean (SD) or *n* (%)
Gender	Women	249 (70.5%)
	Men	104 (29.5%)
Age (years)		45.72 (12.20)
Ethnicity	White	264 (75.9%)
	Black	42 (12.1%)
	Mixed/Other	22 (6.3%)
	Asian	20 (5.7%)
Years of education		13.94 (3.66)
Work status	Unemployed because of pain	188 (54.7%)
	Employed part time due to pain	42 (12.2%)
	Employed full time	34 (9.9%)
	Homemaker	18 (5.2%)
	Unemployed for other reason	8 (2.3%)
	Unpaid volunteer	5 (1.5%)
	Employed part time--other	4 (1.2%)
	Carer	4 (1.2%)
	In other training	4(1.2%)
	Retired	4 (1.2%)
	Student	1 (0.3%)
Pain Duration (years)		13.56 (10.41)
Primary pain location	Lower back/spine	152 (46.5%)
	Generalized	101 (30.9%)
	Lower limbs	31 (9.5%)
	Upper shoulder/limbs	16 (4.9%)
	Neck region	13 (4.0%)
	Head, face or mouth	4 (1.2%)
	Abdominal region	4 (1.2%)
	Pelvic region	3 (0.9%)
	Chest region	2 (0.6%)

Table 2 Mean (M) and standard deviations (SD) at baseline and post-treatment, t values, degrees of freedom, effect sizes (*d*), and p values for baseline to post-treatment changes on study variables.

	Baseline		Post-treatment					
	M	SD	M	SD	*t*	*df*	*d*	*p*
Fatigue (FSS)	48.37	14.07	43.30	13.02	5.68	291	0.37	<.001
Pain intensity	7.61	1.65	6.76	1.73	8.60	299	0.50	<.001
Pain-related interference (BPI)	7.73	1.61	5.71	2.06	17.07	300	1.08	<.001
Work and social adjustment (WSAS)	32.22	5.77	27.53	8.03	11.10	301	0.65	<.001
Depression (PHQ-9)	17.75	5.57	12.62	6.11	15.64	299	0.87	<.001
Pain acceptance (CPAQ-8)	16.89	7.53	22.46	7.59	-11.54	293	0.74	<.001
Cognitive fusion (CFQ-7)	31.18	11.25	30.23	10.50	1.84	291	0.09	0.068
Committed action (CAQ-8)	25.76	8.28	27.18	7.66	-3.18	292	0.18	0.002

Note. When Bonferroni correction was applied (critical a = .0125), all significance levels remained the same. FSS=Fatigue Severity Scale; BPI=Brief Pain Inventory; WSAS=Work and Social Adjustment Scale; PHQ-9=Patient Health Questionnaire Depression Module; CPAQ-8=Chronic Pain Acceptance Questionnaire—8-item version; CFQ=Cognitive Fusion Questionnaire; CAQ-8=Committed Action Questionnaire—8-item version.

Table 3 Pearson's *r* and number of participants included in each analysis (*N*) for the correlations between residualized change scores for fatigue, pain and psychological flexibility processes (pain acceptance, defusion, and committed action), and daily functioning (pain interference, work and social adjustment, and depression).

	FSS	BPI	WSAS	PHQ-9
Pain Severity	0.20**	0.46***	0.33***	0.30***
(N)	*290*	*298*	*300*	*299*
CPAQ-8	-0.46***	-0.39***	-0.44***	-0.40***
(N)	*291*	*293*	*294*	*293*
CFQ	0.32***	0.26***	0.28***	0.42***
(N)	*288*	*291*	*292*	*291*
CAQ-8	-0.36***	-0.31***	-0.29***	-0.40***
(N)	*289*	*292*	*293*	*292*
FSS		0.40***	0.36***	0.41***
(N)		*291*	*292*	*291*

Note.* P<.05, **p<.01, ***p<.001. When Bonferroni correction was applied (critical a = .0125), all significant levels remained the same. CPAQ-8=Chronic Pain Acceptance Questionnaire—8-item version; CFQ=Cognitive Fusion Questionnaire; CAQ-8=Committed Action Questionnaire—8-item version; FSS=Fatigue Severity Scale; BPI=Brief Pain Inventory; WSAS=Work and Social Adjustment Scale; PHQ-9=Patient Health Questionnaire Depression Module.

Table 4 Hierarchical regressions with change in pain severity, pain acceptance, cognitive fusion, and committed action as independent variables, and change in fatigue as dependent variable.

Block	Predictor	*F change*	*df*	R^2	Δ R^2	*β*	*p*
	Fatigue (FSS)						
1	Pain (0-10)	9.68	(1,252)	0.04	0.04	0.14	0.012
2	Pain acceptance (CPAQ-8)	68.11	(1,251)	0.24	0.20	-0.36	<.001
3	Cognitive fusion (CFQ)	6.93	(1,249)	0.27	0.04	0.10	0.114
	Committed Action (CAQ-8)					-0.15	0.020

Note. When Bonferroni correction was applied (critical a = .0125), all significance levels remained the same, except for committed action, which was no longer significant. CPAQ-8=Chronic Pain Acceptance Questionnaire—8-item version; CFQ=Cognitive Fusion Questionnaire; CAQ-8=Committed Action Questionnaire—8-item version; FSS=Fatigue Severity Scale; None of the demographic variables showed significant predictive utility in the model. Therefore, demographic variables were not included in the regression model. The numbers of blocks indicate the order of the blocks in the final hierarchical regression model. Pain was force entered in the first block, pain acceptance the second, and cognitive fusion and committed action were force entered simultaneously into the third block.

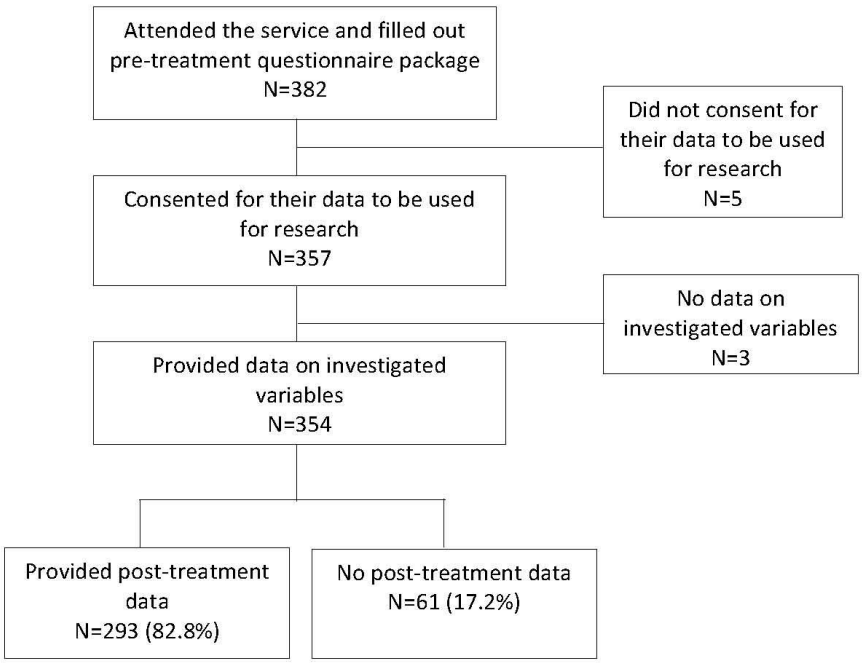

Figure 1 Flowchart of data collection process

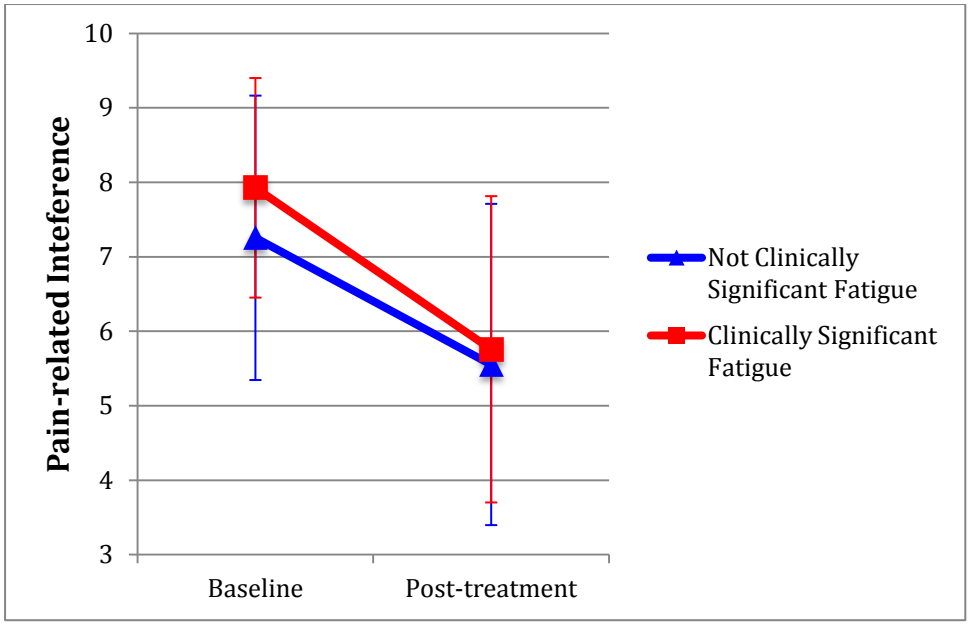

Figure 2 Plot of the Time*Baseline Fatigue Interference Interaction in Relation to Pain Interference.

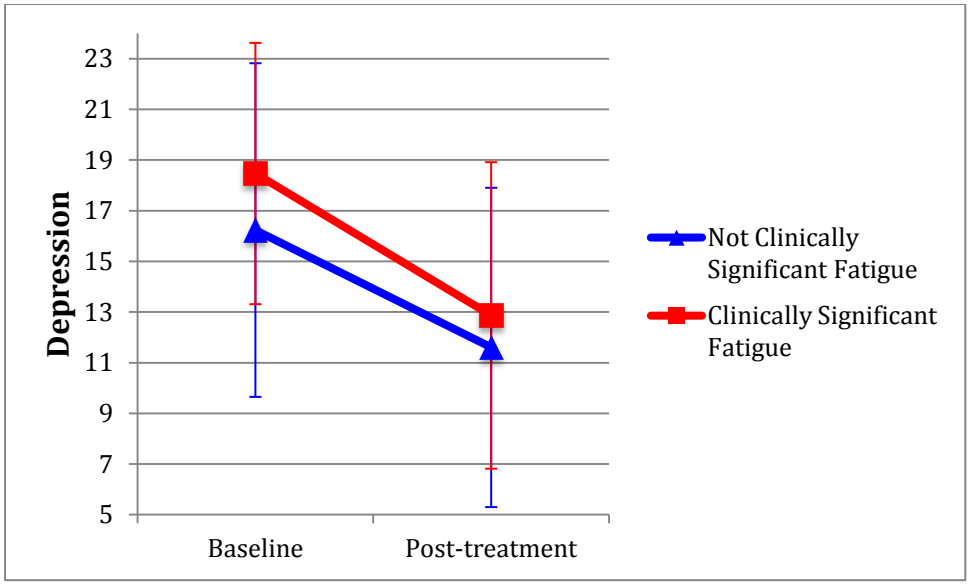

Figure 3 Plot of the Time*Baseline Fatigue Interference Interaction in Relation to Depression